

Guideline for Natural History Studies

Natural history studies are important avenues of investigation that can increase our understanding of disease and lead to important diagnostic and therapeutic advances. With this guideline, we wish to share the IRB's thinking on natural history studies and to assist investigators in preparing protocols for submission.

The FDA has issued [draft guidance](#) on natural history protocols in the context of collecting data to support drug development. While not applicable in its entirety to many NIH protocols, it is a useful guide and provides the following description of a natural history study:

“a preplanned observational study intended to track the course of the disease. Its purpose is to identify demographic, genetic, environmental, and other variables (e.g., treatment modalities, concomitant medications) that correlate with the disease's development and outcomes. Natural history studies are likely to include patients receiving the current standard of care and/or emergent care, which may alter some manifestations of the disease. Disease registries are a frequent platform to acquire the data for natural history studies.”

This captures the spirit of most, if not all the NIH Natural History studies.

Distinguishing clinical care from research in a Natural History Study

A particular challenge in the review of natural history protocols is the close intermingling of clinically driven care with research interventions. In requiring investigators to distinguish between clinical care and research, the IRB's goal is to place the constraints of the research regulations only on those aspects of a natural history protocol that require them; it is not to prevent NIH investigators from providing clinical care within the context of a natural history protocol. To that end, the following descriptions provide a useful framework.

The practice of medicine: “refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.” ([Belmont Report](#))

Research: “designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships)” ([Belmont Report](#))

The human subjects research regulations apply **only** to research, not to the practice of medicine. Activities that are undertaken for an individual patient and driven by the clinical needs of that patient with the intent to diagnose, cure, mitigate, or otherwise treat that person's condition are clinical interventions and, for the purpose of IRB review, are not research. **The only (and very important) exception to this is the use of unapproved drugs or devices.** The FDA does not allow clinical use of unapproved drugs or devices, therefore the use of these is always subject to the research regulations. In contrast, off-label use of an approved drug or device may not be research if the intent is to treat an individual patient and not to study the safety or effectiveness of the drug or device for a new indication.

Is the practice of medicine/clinical care the same as “standard of care (SOC)”? In many cases, clinically driven procedures and interventions that are undertaken in a natural history study are identical to what would be considered standard of care for that condition. For example, obtaining cultures and initiating broad-spectrum anti-microbial therapy in a febrile patient with neutropenia.

However, the defining characteristic of clinical care is not that it is identical to the care that someone might receive in their doctor's office or a non-research hospital. It is that the intervention is designed and intended to benefit that individual patient based upon their specific condition at that time, and is known to have a reasonable chance of success. This may be true even if it is something that is not routinely done at other institutions. For example, an NIH investigator may have access to diagnostic assays or imaging modalities that are known to be more sensitive or specific than those that are available outside of NIH. The use of those assays to diagnose an individual patient/subject's clinical condition and guide therapy does not make them research unless of course, the investigator is testing the safety and effectiveness of those assays. Another example would be the off-label use of an approved drug to treat an individual patient. As mentioned previously, the use of unapproved drugs or devices is always research, as the FDA does not permit their use outside of research or expanded access mechanisms.

How do I describe what I am doing in a natural history protocol?

The protocol document is often described as a recipe and should be written so that a reader can clearly understand how to implement the research. This can be more challenging for a natural history protocol than a clinical trial of a new drug, as not every subject may undergo the same research procedures. Nonetheless, the protocol needs to clearly describe the research procedure(s) in a way that the IRB reviewer can clearly understand what is being done and whether or not the procedure(s) is a research intervention.

It is particularly important to clearly distinguish between activities that may be undertaken for clinical purposes from those that are research. The IRB does not apply the [criteria for approval](#) to clinical care. It may be necessary to describe some of the clinical activities in the protocol to provide context for the research. For example, if additional biopsies are to be taken for research purposes during a clinical procedure, the IRB will need to know what procedure is being performed. However, the protocol and consent do not need to include a complete description of the procedure or the associated procedural risks, instead describe only those risks associated with additional research biopsies.

Research interventions

A natural history protocol may include *systematic research interventions* as well as *secondary data collected during clinical care*. Both should be described in the protocol document and should be clearly distinguished.

Systematic research interventions refer to those activities specified in the protocol that you will perform on all or some subjects based upon protocol-specified criteria. These interventions might be time or event-driven, or specific to a cohort of subjects whose disease presents in a certain way. Systematic interventions enable uniform data collection on the course of the disease under study. Some examples are provided below:

- Yearly brain MRIs on all subjects enrolled in a natural history study of multiple sclerosis
- Pulmonary function tests every 6 months on all patients enrolled on a natural history study of pulmonary hypertension
- Complete blood counts every 3 months on all patients enrolled on a natural history study of immunodeficiency diseases.

- Brain MRIs when subjects enrolled in a natural history study of MS experience a pre-specified change in functional status
- Bone marrow biopsies on patients enrolled in a natural history study of myelodysplastic syndrome when the white blood cell count exceeds a pre-specified threshold.

Although these may be similar or even identical to the interventions that a clinician might perform outside the research context, because the investigator has specified in the protocol that these will be done in a systematic and protocol-driven manner, for the purposes of IRB review they are research interventions, and as such, the IRB will consider their risks and benefits.

Systematic interventions should be completely described in the protocol and consent. This should include a description of the intervention and the associated risks. The intervention should be listed in the schedule of activities. For interventions that may occur a variable number of times depending on the status of the subject, it may be important to place some parameters on the frequency. For example, if a protocol specifies a CT scan will be done every time the subject experiences a particular symptom or lab abnormality, an upper annual limit should be specified so that the IRB can determine that subjects will not be placed at an unreasonable level of risk due to excessive radiation exposure.

Data collection during clinical care

In many natural history protocols, the investigator is also providing clinically driven care to the subject. This may include a wide range of diagnostic and therapeutic interventions and may include activities viewed as the routine practice of medicine as well as some that may not necessarily be standard of care, since there may not be a standard of care for that condition. The important feature that distinguishes this from research is that it is an *individualized decision* made for a given patient (presumably in that person's best interest) and it is *not specified as a systematic intervention/procedure in the protocol*. The IRB does not consider this to be research and does not assess the risk/benefit of this intervention.

The data obtained from these interventions is very likely to be important in achieving the objectives of a natural history study. Therefore, the investigator will almost certainly want to access that data for research purposes. This is entirely permissible and encouraged. In this case, the research activity is the accessing of clinically collected data, not the clinical intervention itself. The researcher should describe in the protocol that they will access and analyze clinical medical record data as part of the research. They should describe the sources of that data (i.e., CRIS if at NIH) and if it will include data collected at other institutions.

Mixed clinical/research interventions

In some natural history protocols, a research intervention is inextricably linked to a clinical intervention. For example, a decision to perform a diagnostic procedure may be driven entirely by the clinical needs of the subject. However, during the clinical procedure, additional testing or interventions may be done for research purposes. An example of this would be the decision to perform a tissue biopsy that is clinically driven, but at the time of the procedure, extra biopsies are taken for research. Another example would be a clinical decision to do an MRI on a patient, but while they are having the clinical scan, additional research sequences are also performed.

Examples scenarios of research vs clinically driven care in a natural history study

1. A researcher follows subjects with immunodeficiency syndromes in a natural history study. The protocol specifies that subjects will have blood work performed every 6 months and a CT of the chest performed annually to assess the extent of bronchiectasis. Subjects are also seen on an as-needed basis if there is clinical deterioration, and the investigator orders additional diagnostic procedures or provides therapies as clinically indicated. The data from the clinical interventions will be collected and analyzed for research purposes.

In this protocol, the 6-month blood work and annual CT of the chest are considered research interventions, as they are systematically obtained on all subjects and driven by the requirements of the protocol. These procedures should be described as such in the protocol and consent, listed on the schedule of activities, and all associated risks delineated.

The secondary collection and analysis of the clinical data from subjects that are seen during an acute deterioration is also research. However, the clinically indicated procedures and therapy are not research and, therefore, those procedures and therapies do not need to be described in detail nor do the risks need to be described in the protocol. The protocol should contain language to this effect. For example:

“If subjects undergo diagnostic testing or treatment for clinical purposes, the medical record data will be collected and analyzed for research purposes so that we may gain a full characterization of the disease. This includes all laboratory and imaging data from the NIH Clinical Center”

The risk associated with the secondary collection and analysis of the clinical data is a breach of confidentiality, and that risk should be described in the protocol and consent.

2. A researcher follows subjects with hypereosinophilia syndromes. All subjects are seen annually and may have added as-needed visits if they experience a clinical deterioration. At the annual visits, all subjects undergo a history and physical exam, blood work, and a bone marrow biopsy. At interim visits, diagnostic procedures and therapeutic interventions will only be done as clinically indicated. However, if the subject undergoes a clinically indicated procedure with biopsies, additional biopsies may be taken for research purposes. Clinical procedures that are commonly required include GI endoscopy, bronchoscopy, skin, soft tissue, or muscle biopsies.

The annual history and physical exam, blood work, and bone marrow biopsy are all systematic interventions driven by the protocol and are considered research for the purposes of IRB review, even if they would normally be done in a clinical setting. These should be listed in the schedule of activities, and fully described in the protocol and consent.

As with the prior example, the secondary collection and analysis of clinical data is research but the actual clinical interventions are not. Unlike the prior case, however, there may be some additional biopsies taken during the procedure. Those biopsies are research, and any incremental risk associated with them must be described in the protocol and consent. Example language for this scenario is below:

Protocol:

Collection of additional tissue or biological fluid samples: Additional tissue or biological fluid samples may be obtained from consenting adult and pediatric subjects undergoing clinically indicated endoscopy/colonoscopy, bronchoscopy, or skin/soft tissue/muscle biopsy for diagnostic purposes or to assess response to therapy. Additional biopsies will be performed for research only if there is minimal additional risk to the participant, as assessed by the clinician performing the procedure. Based on data from the literature (see Risks section), gastrointestinal biopsies for research will be limited to 6 per segment in adults and a total of 4 from all segments combined in children. Research biopsies from other tissues will be limited to 3 per site. Research biopsy samples will be used for the assessment of factors involved in eosinophil migration to the tissue and disease pathogenesis.

Consent:

Tissue biopsies: You may have biopsies as part of your standard medical care. We will explain the procedure in full to you at the time and have you sign a standard hospital consent document. When available, we will ask to use any leftover tissue or body fluid sample for research tests. We may also ask your permission to collect a few extra samples just for research during the following procedures if they are performed for clinical reasons to diagnose or monitor your eosinophilic disorder: these may include endoscopy/colonoscopy, bronchoscopy, or skin/soft tissue/muscle biopsy. The risk of the extra biopsies is very small, for example, there may be some bleeding. The risks of the additional biopsies are the same as the standard clinical biopsy and will be described to you at the time you provide the clinical consent for the procedure. If you decide that you do not want extra research samples to be taken, this will not affect your standard medical care or participation in this protocol. Our research tests include looking to see if eosinophils are present in different tissues, and how your disease affects these tissues.

What constitutes a benefit in a natural history protocol?

Just as the IRB only assesses the risks of the research interventions and not the clinical care, it only assesses the benefits associated with the research procedures. It is presumed that any clinically driven procedure or therapy is provided to a given subject because the physician believes it has the potential to benefit a patient, as that is a fundamental premise of the practice of medicine. When balancing the risk: benefit ratio of a protocol, the IRB will only weigh the risks of the research interventions against the benefits of those same interventions. The IRB recognizes that while subjects may benefit from the clinical care they receive as a patient enrolled in the natural history study, that benefit is not due to the research per se and therefore is not used to balance against the research risks.

If a research procedure does have the potential to directly benefit the subject, this should be clearly described in the protocol. That benefit might be a directly therapeutic (e.g., administration of a drug effective in the disease), or monitoring of the subject's condition in a way that will permit an earlier or more effective therapeutic intervention than would happen outside the context of the research, even if the therapy per se is not part of the research.

For example, in the natural history study of eosinophilic diseases, subjects undergo clinically indicated endoscopic procedures with the addition of extra research biopsies. If those extra research biopsies are taken to the lab and just frozen for future studies, there is no direct benefit associated with obtaining them. However, if those same biopsies are analyzed by the investigator

in real-time, and the results of that analysis can directly inform the clinical care of the subject, then it is possible that the IRB could consider there to be a prospect of direct benefit. This would be dependent on the strength of the evidence provided by the investigator that the analysis of the biopsy has clinical utility. This would need to be clearly described in the protocol and supporting evidence provided.

For studies enrolling only adults, whether or not a research procedure provides the prospect of direct benefit is not critical, as the IRB is permitted to weigh the research risks solely against the importance of the knowledge to be gained. However, in studies enrolling children (or decisionally impaired adults if at an NIH site), **this is critical** as there are additional regulatory and policy constraints.

Reporting requirements for Natural History Studies

The reporting requirements for all human subjects research are described in [Policy 801-Reporting Research Events](#). These requirements do not differ for natural history studies. In addition to those events that require expedited reporting via the Reportable Event Form (REF), the IRB requires that investigators provide a high-level summary of adverse events and serious adverse events that do not meet the definition of an unanticipated problem at the time of continuing review. This has led to some confusion as to whether investigators are required to track and record all AEs and SAEs in a research database for all subjects that are enrolled in the natural history study, and whether the IRB can grant an “exception” to AE reporting requirements.

The IRB does not grant exceptions to any reporting requirements. The IRB reporting requirements do not mandate that investigators track and record in a database every AE/SAE experienced by a subject enrolled in a natural history study. Given that many of these studies follow subjects with chronic medical conditions, the majority of the AEs/SAEs are likely to be related to the underlying disease and not to the research itself.

Investigators should track and record AEs and SAEs that are related to the research procedures in a research database. Furthermore, if a research intervention or procedure is known to commonly lead to mild adverse events, for example, grade 1 or 2 hot flashes following administration of IV contrast for a CT scan, it may not be particularly useful to record that AE in the database.

Investigators should describe in the data collection section of the protocol whether and how they intend to track AEs and SAEs. Data should be collected that is needed to report/track the safety of the research interventions/procedures and that is needed for any future publication. In addition, data that is required by any external sponsor or regulatory authority should also be collected in the database. For example, it may be appropriate to include text to the effect of:

AEs and SAEs that are related to the research procedures described in this protocol will be recorded, except for Grade 1 or 2 AEs that are expected. AEs and SAEs that in the investigators' judgment are not at least possibly related to research procedures, for example, those that are due to the natural course of the disease, will not be recorded as AEs/SAEs in the research database.

Statistical Analysis Plan (SAP)

Natural history studies are by their very nature exploratory and hypothesis-generating. Nonetheless, a well-designed natural history study should include a statistical analysis plan (SAP) when feasible. The draft [FDA guidance](#) on natural history studies includes the following

information on the SAP. Investigators should include in their protocol an SAP that addresses these points as much as is possible.

The SAP elements should delineate the analysis population, definition of endpoints, descriptive objectives, testable hypotheses and statistical methods to be employed in analysis of the data including the timing of the data analyses conducted in the study. The SAP should include enough detail so that the analysis results can be replicated. The SAP can also increase the study's efficiency by focusing on the most relevant data to be collected without imposing excessive rigidity (Thomas and Peterson 2012). Preplanned interim analyses at certain intervals or milestones may suggest design changes to the protocol. Protocol elements may be modified or dropped for reasons of relevancy, feasibility, and reliability based on interim analyses, but any such changes should be well documented as an amendment to the protocol, including the timing and rationale for the changes.

In any natural history study, consistency of procedures and data collection across data collection sites and across time is critical. The analysis model may also need to make adjustments for the effects of sites within the country or region. A natural history study that collects data in widely dispersed site locations needs to consider potential language and cultural differences in the patient perceptions, manifestations, and effects of a disease. Evaluation of intra- and inter-rater reliability of clinical outcome assessments and performance requirements of the biomarker measurement assays/tests should be considered.

The above section is provided as an example and may not be applicable to all natural history studies. For example, if only descriptive statistics are feasible, at a minimum these should be described.

Human Subjects Protections

All studies supported or conducted by the NIH are subject to the Common Rule ([45 CFR 46](#)) and some natural history studies may also be subject to FDA regulations if they meet the [FDA definition of a Clinical Investigation](#). Thus, unless exempt, the same human subjects protections requirements apply to a natural history study as any other study, and the protocol needs to address them.

Informed consent

All subjects enrolled in a natural history study must provide informed consent for participation unless consent has been waived by the IRB. If children are enrolled, parental permission and the child's assent must be obtained unless waived by the IRB.

The close intermingling of clinical care and research interventions may pose some challenges for creating the informed consent document. A guiding principle that should be considered when writing the document is that consent should allow the subject to clearly understand and distinguish between the aspects of their participation that are research from those that they might ordinarily experience during routine clinical care for their condition.

The procedures and interventions that are described in the protocol as research, (i.e., systematic research interventions, secondary clinical data collection) should be completely described in the

consent along with their attendant risks. Clinical procedures that are solely driven by the clinical needs of the subject (and therefore are not considered research) should not be described in the consent. The IRB recognizes that some description may be necessary to provide an understandable context for the subject, but detailed descriptions of purely clinical procedures should not be included in the consent document.

Protecting Confidentiality

As many natural history studies are primarily observational, protecting the confidentiality of the data may be the major human subjects protections concern, and a breach of confidentiality may be the major risk of the study. Investigators should describe in their protocol how data will be protected. Research data collected by NIH investigators are subject to the Privacy Act and other policy and regulatory requirements (e.g., Certificates of Confidentiality). Although NIH is not subject to HIPAA, if data is being accessed from other institutions, it is possible that HIPAA applies to data that is accessed and investigators should determine if releases from the other institutions are necessary before accessing outside medical records.

Collecting family history and enrolling family members

Many natural history studies collect extensive information about the subject's relatives, and often wish to enroll family members as controls or if affected with the same condition, as subjects. Several issues need to be considered in both of these scenarios.

Family History Questionnaires

If the family medical history is collected in an identifiable manner, it is possible that the family member must now be considered a subject in the research. The regulatory justification for this is found in the definition of a human subject:

(e)(1) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research:

- (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Therefore, if it is scientifically feasible, it is best to collect the information without identifiers. If you must obtain identifiers, then you must either obtain the informed consent of the family member (meaning the person that the information is about) or request a waiver of informed consent from the IRB.

You must include in your submission to the IRB the family history questionnaire that you will be using so that the IRB can determine if the family member is, in fact, a human subject participant in the research, and whether or not informed consent is required or can be waived. The questionnaire should collect only that information about the family member which is scientifically necessary, especially if a waiver of informed consent is being requested. If a waiver of informed consent is requested, it must satisfy all of the [regulatory criteria for a waiver of consent \(45 CFR 46.116\(f\)\(3\)\)](#).

Enrolling family members

If you wish to enroll family members, several factors must be considered, starting with how the family members will be recruited. If you are enrolling only the immediate family members of the proband, this is less of a concern. However, if you wish to contact and enroll more distant relatives, some privacy issues must be addressed.

Family members may not be aware that their relative is enrolled in a study and may or may not be supportive of having had their private information disclosed to an individual without their permission. This is especially true if information about their medical history has been disclosed by the proband prior to contacting the relative.

The best practice is to request that the proband contact their family members about the study. The proband can provide an IRB-approved information sheet to the family members to inform them about the study and let them know they may be contacted. If a family member requests not to be contacted, this wish must be respected by the research team.

If it is not possible to have the proband contact the family members ahead of time, you must describe in the protocol how family members will be contacted. Will the contact be by phone, email, or US postal service? Any verbal scripts or written material sent to the family members must be submitted to the IRB for review and approval before being used. Only the minimum amount of essential information should be collected about the relative before the contact and obtaining of consent. Investigators are expected to protect the privacy of the relatives, and if the relative declines participation in the study, any identifiable information collected about them should be destroyed.